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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/540,466	03/31/2000	UGO RIPAMONTI	STK-6	2489

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EXAMINER	
NICKOL, GARY B	
ART UNIT	**PAPER NUMBER**
1642	10

DATE MAILED: 12/18/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/540,466	Applicant(s) RIPAMONTI ET AL.	
	Examiner Gary B. Nickol Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-17 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-17 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

The Amendment filed September 25, 2001 (Paper No. 9) in response to the Office Action of June 19, 2001 is acknowledged and has been entered. Claims 1, 18 and 20 have been cancelled. Claims 2-17, and 19 are pending and are currently under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Withdrawn

The rejection of Claims 6, 8, 10, 13-16 under 35 U.S.C. 112, first paragraph, scope of enablement is withdrawn. Applicants argue (Paper No. 9, page 11) that it would be routine for one of skill in the art to determine whether an amino acid variant of a morphogenic protein is capable of inducing angiogenesis or whether an amino acid variant of a morphogenic protein stimulatory factor is capable of improving the angiogenic inductive activity of a morphogenic protein. Applicants assert that the specification provides examples (pages 51-53) which may be used to determine the above. This argument has been considered and is found persuasive.

Rejections Maintained

Claims 2, 4-6, 9-14, 16-17, and 19 remain rejected under 35 U.S.C. 102(b) as being anticipated by Duneas et al. (Growth Factors, Vol. 15, 1998, pages 259-277, IDS) for the reasons of record in Paper No. 8, pages 7-8.

Applicants argue (Paper No. 9, page 12) that the data presented by Duneas *et al.* do not demonstrate that treatment with OP-1 and TGF-β1 results in enhanced vascularization over TGF-β1 or OP-1 alone. This argument has been considered but is not found persuasive. Duneas *et al.* clearly teach (page 274, column 1) that the "many-fold increase in type IV collagen mRNA synthesis over a single application of hOP-1 and TGF-β1, suggests that the two morphogens interact synergistically to induce angiogenesis and vascular invasion. Applicants counter this by arguing that there is nothing in Duneas *et al.* to "demonstrate" that type IV collagen expression is required for angiogenesis and that at best, the data suggests that their may be a correlation between collagen IV mRNA expression and enhanced vascularization. This argument has been considered but is not found persuasive. On the contrary, Duneas *et al.* teach that angiogenesis is a prerequisite for osteogenesis. Further, the analysis of type IV collagen mRNA was not the only parameter used to assess tissue morphogenesis (see pages 268-269, Duneas *et al.*). Other parameters include the observation that binary applications of hOP-1 and pTGF-β1 resulted in synergistic induction of tissue morphogenesis as determined by histology and histomorphometry. Further, Duneas *et al.* clearly teach that co-administration of hOP-1 and pTGF-β1 induced bone morphogenesis several fold greater than the sum of the effect of both morphogens implanted singly" (Duneas *et al.* , page 274, column 1). Hence, since angiogenesis is a prerequisite for osteogenesis, the application of both hOP-1 and pTGF-β1 inherently improved the angiogenic

inductive activity by co-administering both proteins. Thus, applicants arguments have not been found persuasive, and the rejection is maintained.

Claims 2-5, 7, and 12-15 remain rejected under 35 U.S.C. 102(e) as being anticipated by Goldberg et al. (US Patent 6,013,624; October 1993, IDS) as evidenced by Amano et al. (Arch Oral Biol., Vol. 44, No. 11, November 1999, abstract only) for the reasons of record in Paper No. 8, pages 9-10.

Applicant argue (Paper No. 9, page 13) that scatter factor (hepatocyte growth factor), as taught by Goldberg *et al.* is NOT a morphogenic protein. Applicants argue that scatter factor is a "morphogenic protein stimulatory factor". Applicants argue that both scatter factor and FGF are defined in the instant application as morphogenic protein stimulatory factors and neither protein is included in the definition of a morphogenic protein. This argument has been considered but is not found persuasive. The specification defines (page 13, line 24+) a morphogenic protein as one having morphogenic activity. "For instance, this protein is capable of inducing progenitor cells to proliferate and or to initiate differentiation pathways that lead to the formation of cartilage, bone, tendon, ligament, vascular, neural or other types of tissue...". And, Goldberg *et al.* (column 1, lines 40-44) teach that "scatter factor induces kidney epithelial cells in a collagen matrix to form branching networks of tubules, suggesting that it can also act as a morphogen" . Furthermore, as evidenced by van der Wee *et al.* (Exp. Cell. Res., Vol. 252, No. 1, October 1999, abstract only) and Michalopoulos *et al.* (J.Cell Physiol., Vol. 156, No. 3, 1993, abstract only) scatter factor (or hepatocyte growth factor) is considered by those of skill in the art to be a morphogenic protein. Thus, applicants have not provided sufficient evidence of the

contrary; that scatter factor (hepatocyte growth factor) is NOT a morphogenic protein. Furthermore, while the claims are to be interpreted in light of the specification, it does not follow that limitations from the specification may be read into claims. On the contrary, claims must be interpreted as broadly as their terms reasonably allow. See Ex parte Oetiker, 23 USPQ2d 1641 (BPAI, 1992). Applicant is reminded that the claims define the subject matter of his invention and that the specification cannot be relied upon to read limitations into the claims. Thus, applicants arguments have not been found persuasive, and the rejection is maintained.

Claims 2-5, 7, 12-15, and 17, 19 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Goldberg et al. (US Patent 6,013,624; October 1993, IDS) as evidenced by Amano et al. (Arch Oral Biol., Vol. 44, No. 11, November 1999, abstract only) for the reasons of record in Paper No. 8, pages 11-12.

Applicants arguments are substantially the same as above with regards to Goldberg *et al.* Thus, for the reasons of record, the rejection is maintained.

NEW REJECTIONS

Claim Rejections - 35 USC § 112

Claims 6, 8, 10, 13-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed,

had possession of the claimed invention. The written description in this case only sets forth a morphogenic protein comprising an amino acid sequence selected from the group consisting of OP-1 (elected species, Paper No. 7, page 3) or a morphogenic protein stimulatory factor which comprises at least one compound selected from the group consisting of bFGF (elected species, Paper No. 7, page 4) and therefore the written description is not commensurate in scope with the claims which read on allelic variants of the elected species. Support for naturally occurring variants, that is allelic variants, is provided in the specification on page 17, line 8 where it is disclosed that morphogenic proteins include biologically active variants of any known morphogenic protein, including variants containing conservative amino acid changes or on page 47, line 27 where a preferred morphogenic protein stimulatory factor is bFGF and amino acid variants thereof. This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

What are allelic variants? Reiger et al. (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome..... and

differing from other alleles of that locus at one or more mutational sites (page 17), which therefore encode allelic variant proteins. Thus, the structure of naturally occurring allelic sequences are not defined, nor in this case, is the structure of allelic variant proteins encoded by allelic variant genes defined. With the exception of OP-1 or bFGF, the skilled artisan cannot envision the detailed structure of the encompassed polypeptides and or encoded variants and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The amino acid sequence itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016. Although these court findings are drawn to DNA art, the findings are clearly applicable to the claimed proteins.

Furthermore, although drawn to the DNA art, the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly applicable to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Therefore only a morphogenic protein comprising an amino acid sequence selected from the group consisting of OP-1 or a morphogenic protein stimulatory factor which comprises at least one compound selected from the group consisting of bFGF meets the written description provision of 35 USC 112, first paragraph.

All other rejections/objections are withdrawn.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
December 12, 2001